

1048

April 6, 2000

Dockets Management Branch (HFA-305) Food and Drug Administration 5600 Fishers Lane Room 4-62 Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this Petition, pursuant to Section 505(i)(2)(c) of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 C.F.R. Sections 314.93(b) and 10.30 of the Food and Drug Administration's regulations. to request the Commissioner of Food and Drugs to make a determination that a certain opioid analgesic elixir drug product is suitable for filing under an abbreviated new drug application (ANDA).

A. Action Requested

Petitioner requests that the Commissioner of Food and Drugs make a determination that an abbreviated new drug application (ANDA) is suitable for elixirs containing 10 mg hydrocodone bitartrate/325 mg acetaminophen per 15 mL. 10 mg hydrocodone bitartrate/500 mg acetaminophen per 15 mL, and 10 mg hydrocodone bitartrate/650 mg acetaminophen per 30 mL.

B. Statement of Grounds

The Drug Price Competition and Patent Term Restoration Act of 1984 ("the Waxman-Hatch Act") extends eligibility for the submission of ANDA's to certain drug products identical to those approved via new drug applications, as identified in the List of Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") published by the Food and Drug Administration. Where the proposed drug product differs from the "listed drug" in one or more respects, a person may petition the Agency, under section 505(j)(2)(c) of the Act, for a determination that the proposed drug is suitable to be submitted as an ANDA.

The listed drug product that forms the basis for this petition Norco™.10 mg/325 mg,(ANDA 40-148, manufactured by Watson Labs) Watson 10 mg/500 mg, (ANDA 40-148) Watson,10 mg/650 mg (ANDA 40-094). See Orange Book, page 3-4 and 3-3, at Exhibit A. To the best of petitioner's knowledge, applicable U.S. patents with respect to the drug substances, hydrocodone bitartrate and acetaminophen, have expired.

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The proposed drug product differs from the listed drug products only in regard to dosage form (elixir instead of tablet). Otherwise, the proposed drug product is identical with respect to active ingredients, strength, route of administration, and conditions of use.

The availability of an elixir dosage form of hydrocodone bitartrate and acetaminophen would provide a valuable dosage alternative, particularly for those patients who have trouble swallowing tablets, the geriatric population and other situations where a liquid dosage would be preferred.

The proposed product's dosage form is the same as several other types of approved opioid analgesic drugs which are available in liquid form. For instance, Capital and Codeine (acetaminophen and codeine), NDA 85883 (*Orange Book* at 3-2); Dilaudid (hydromorphone hydrochloride), NDA 19891 (*Orange Book* at 3-182); and Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir), ANDA 81051 (*Orange Book* at 3-4) attached as Exhibit B.

In view of the availability of other approved opioid analgesics as elixirs and an appropriate patient base for such a form (e.g., geriatric patients), the healthcare community would benefit from the availability of an elixir dosage form of hydrocodone bitartrate and acetaminophen 10 mg/325 mg per 15 mL, 10 mg/500 gm per 15mL, and 10 mg/650 mg per 30 mL. The proposed product contains the same active ingredients, at the same strength and route of administration, and would be labeled with the same conditions of use as the listed 10 mg/325 mg, 10 mg/500 mg, and 10mg/650 mg tablets [See Exhibits C (Side-By-Side comparison of Watson and Norco inserts and proposed insert) and D (Side-By-Side comparison of Watson and Norco labeling and proposed labeling)] and packaged in an appropriate container-closure system (See Exhibit E).

Based on the foregoing, Petitioner believes that an elixir dosage form of hydrocodone bitartrate and acetaminophen 10 mg/325 mg per 15 mL, 10 mg/500 gm per 15mL, and 10 mg/650 mg per 30 mL warrants a finding of ANDA suitability and that the commissioner should grant permission for the filing of an ANDA for a hydrocodone bitartrate and acetaminophen elixir in the strengths of 10 mg/325 mg per 15 mL, 10 mg/500 mg per mL, and 10 mg/650 mg per 30 mL.

C. Environmental Impact

A categorical exclusion is claimed as the granting of this Petition will result in an ANDA for a drug product that is consistent with the parameters for exclusion established in 21 C.F.R. 25.24(c)(1).

D. Economic Impact

Information under this section will be submitted if requested by the Commissioner following review of this Petition.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views upon which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

PHARMACEUTICAL ASSOCIATES, INC.

By: Kaye B. McDonald

Company Raye B. McDonald 201 Delaware Street Greenville, SC 29605 (864) 277-7282 Ext. 230

Enclosures:

- A. Orange Book, page 3-5.
- B. Orange Book, pages 3-2, 3-4, and 3-182.
- C. Side-By-Side comparison of Watson and Norco™ package insert (May 1998 and December 1997) and proposed insert.
- D. Side-By-Side comparison of Watson and Norco™ and labeling and proposed labeling for hydrocodone bitartrate and acetaminophen 10 mg/325 mg per 15 mL, 10 mg/500 mg per 15 mL, and 10 mg/650 mg per 30 mL elixir.
- E. Description of container and closure system for hydrocodone bitartrate and acetaminophen 10 mg/325 mg per 15 mL, 10 mg/500 mg per 15 mL, and 10 mg/650 mg per 30 mL elixir.

Exhibit A

ACETAMINOPHEN; HYDROCODONE BITARTRATE

ACETAMINOPHEN; HYDROCODONE BITARTRATE					TAMINOPHEN; HYDROCODON	E BITARTRATE	
ACE	TAMINOPHEN; HIDROCOBONE		ABLET; ORAL				
T	ABLET; ORAL			T	VICODIN ES		
	HYDROCODONE BITARTRATE	AND ACETAMINOPHEN	N40143 001	AA	+ KNOLL PHARM	750MG; 7.5MG	N89736 001
AA	VINTAGE PHARMS	650MG; 10MG	FEB 22, 1996	-			DEC 09, 1988
<u>AA</u>	·	750MG; 7.5MG	N40157 001 APR 12, 1996	<u>AA</u>	VICODIN HP KNOLL PHARM	660MG; 10MG	N40117 001 SEP 23, 1996
<u>AA</u>	WATSON LABS	500MG; 2.5MG	N40123 003 MAR 04, 1996				322 43, 200
<u>AA</u>		500MG; 2.5MG	N81079 001 AUG 30, 1991	ACE	TAMINOPHEN; OXYCODONE		
<u>AA</u>		500MG; 5MG	N40122 001 MAR 04, 1996	c	APSULE; ORAL OXYCODONE AND ACETAMI	NODHEN	
<u>AA</u>		500MG; 5MG	N89883 001 DEC 01, 1988	<u>AA</u>	HALSEY	500MG; 5MG	N40219 001 JAN 22, 1998
<u>AA</u>		500MG: 7.5MG	N40123 004 MAR 04, 1996				
<u>AA</u>		500MG; 7.5MG	N81080 001 AUG 30, 1991	ACE	ETAMINOPHEN; OXYCODONE	HYDROCHLORIDE	
AA		500MG; 10MG	N40148 002 FEB 14, 1997	C	CAPSULE; ORAL OXYCODONE AND ACETAMI	NOPHEN	-
<u>AA</u>		650MG; 7.5MG	N40094 001 SEP 29, 1995	<u>AA</u>	AMIDE PHARM	500MG; 5MG	N40199 001 DEC 30, 1998
<u>AA</u>		650MG; 7.5MG	N40123 001 MAR 04, 1996 N40094 002	AA	MALLINCKRODT	500MG; 5MG	N40257 001 AUG 04, 1998
<u>AA</u>		650MG; 10MG /	SEP 29, 1995 N40123 002	<u>AA</u>	VINTAGE PHARMS	500MG; 5MG	N40106 001 JUL 30, 1996
AA		650MG; 10MG	MAR 04, 1996 N40122 002	<u>AA</u>	WATSON LABS	500MG; 5MG	N40234 001 OCT 30, 1997
<u>AA</u>		750MG; 7.5MG	MAR 04, 1996 N81083 001	AA	ROXILOX ROXANE	500MG; 5MG	N40061 001
<u>AA</u>		750MG; 7.5MG	AUG 30, 1991				JUL 03, 1995
AA	ZENITH GOLDLÍNE	500MG; 5MG	N89696 001 APR 21, 1988	AA	+ JOHNSON RW	500MG; 5MG	N88790 001 DEC 12, 1984
<u> AA</u>	LORTAB MALLINCKRODT	500MG; 5MG	N87722 001 JUL 09, 1982		SOLUTION; ORAL		
	+ UCB	500MG; 10MG	N40100 001	,	ROXICET	325MG/5ML;5MG/5ML	N89351 001
<u>AA</u>	T 0CB	325MG; 5MG	JAN 26, 1996 N40099 001		ROXANE	323MG/ 3MH, 3MG/ 3MH	DEC 03, 1986
	wapaa		JUN 25, 1997		TABLET; ORAL		
	NORCO + WATSON LABS	325MG;10MG 🗸	N40148 001 FEB 14, 1997	<u>AA</u>	OXYCET MALLINCKRODT	325MG; 5MG	N87463 001 DEC 07, 1983
<u>AA</u>	+ KNOLL PHARM	500MG; 5MG	N88058 001 JAN 07, 1983	<u>AA</u>	OXYCODONE AND ACETAM DURAMED	INOPHEN 325MG;5MG	N40272 001 JUN 30, 1998
		•					

Exhibit B

ACETAMINOPHEN; BUTALBITAL; CAFFEINE ACET.					CETAMINOPHEN; CAFFEINE; DIHYDROCODEINE BITARTRATE			
CAPSULE; ORAL					CAPSULE; ORAL ACETAMINOPHEN, CAFFEINE, AND DIHYDROCODEINE BITARTRATE			
AB	ROBERTS AND HAUCK	325MG; 50MG; 40MG	N87628 001 OCT 01, 1986	<u>AA</u>	MIKART	356.4MG; 30MG; 16MG	N40109 001 AUG 26, 1997	
AB	BUTALBITAL, ACETAMINOP WEST WARD	HEN AND CAFFEINE 500MG; 50MG; 40MG	N40261 001 OCT 28, 1998	<u>AA</u>	+ PURDUE FREDERICK	356.4MG; 30MG; 16MG	N88584 001 MAR 04, 1986	
370	BUTALBITAL, ACETAMINOP	HEN, CAFFEINE 325MG:50MG:40MG	N88758 001				•	
AB	ESGIC-PLUS	323113, 33113, 23113	MAR 27, 1985	AC	ETAMINOPHEN; CODEINE PH	OSPHATE		
AB	+ MIKART	500MG; 50MG; 40MG	N40085 001 MAR 28, 1996		CAPSULE; ORAL PHENAPHEN W/ CODEINE	NO. 2 325MG:15MG	N84444 001	
AB	FEMCET MALLINCKRODT	325MG; 50MG; 40MG	N89102 001 JUN 19, 1985		+ ROBINS AH PHENAPHEN W/ CODEINE + ROBINS AH		N84445 001	
AB	TRIAD MALLINCKRODT	325mg;50mg;40mg	N89023 001		PHENAPHEN W/ CODEINE + ROBINS AH		N84446 001	
_		4	JUN 19, 1985	SOLUTION; ORAL ACETAMINOPHEN AND CODEINE PHOSPHATE				
1	ABLET; ORAL BUTALBITAL, ACETAMINOP	HEN AND CAFFEINE		AA	ALPHARMA	120MG/5ML;12MG/5ML 120MG/5ML;12MG/5ML	N85861 001 N40119 001	
AB	MALLINCKRODT	325MG; 50MG; 40MG	N87804 001 JAN 24, 1985	AA	HI TECH PHARMA	120MG/3ML; 12MG/3ML	APR 26, 1996	
AB	MIKART	325MG; 50MG; 40MG	N89175 001 JAN 21, 1987	AA	MIKART	120MG/5ML: 12MG/5ML	N89450 001 OCT 27, 1992	
<u>AB</u>	+	500MG; 50MG; 40MG	N89451 001 MAY 23, 1988	<u>AA</u>	MORTON GROVE MOVA	120MG/5ML;12MG/5ML 120MG/5ML;12MG/5ML	N87006 001 N40098 001 SEP 20, 1996	
AB	WATSON LABS	500MG; 50MG; 40MG	N40267 001 JUL 30, 1998 N89718 001	<u>AA</u>	PHARM ASSOC ACETAMINOPHEN W/ CODE	120MG/5ML; 12MG/5ML	N87508 001	
AB	WEST WARD BUTALBITAL, APAP, AND	325MG; 50MG; 40MG	JUN 12, 1995	AA	ROXANE TYLENOL W/ CODEINE	120MG/5ML; 12MG/5ML	N86366 001	
AB	HALSEY	325MG; 50MG; 40MG	N89536 001 FEB 16, 1988	AA	+ JOHNSON RW	120MG/5ML; 12MG/5ML	N85057 001	
AB	FIORICET + NOVARTIS	325MG; 50MG; 40MG	N88616 001 NOV 09, 1984	AA	SUSPENSION; ORAL ACETAMINOPHEN AND COL CARNRICK	EINE PHOSPHATE 120MG/5ML;12MG/5ML	N86024 001	
			NOV 03, 1304	AA	CAPITAL AND CODEINE ALPHARMA	120MG/5ML; 12MG/5ML	N85883 001	
ACETAMINOPHEN: BUTALBITAL: CAFFEINE; CODEINE PHOSPHATE					TABLET; ORAL			
(CAPSULE; ORAL	•		3.2	ACETAMINOPHEN AND COL	EINE PHOSPHATE 300MG;15MG	N40223 001	
	FIORICET W/ CODEINE + NOVARTIS	325MG; 50MG; 40MG; 30MG	N20232 001	AA	POKAMED		NOV 18, 1997	
	, MOAMITTO		JUL 30, 1992	AA		300MG; 30MG	N40223 002 NOV 18, 1997	

ACETAMINOPHEN; HYDROCODONE BITARTRATE							
ACE	TAMINOPHEN; HYDROCODONE	BITARTRATE			TABLET; ORAL		
					HYDROCODONE BITARTRATE	AND ACETAMINOPHEN	
E	LIXIR; ORAL HYDROCODONE BITARTRATE	AND ACETAMINOPHEN 500MG/15ML; 7.5MG/15ML	√ N81051 001	AA	EON	750MG; 7.5MG	N40149 002
AA	+ MIKART	500MG/15ML; 1.5MG/252	AUG 28, 1992		HALSEY	500MG; 5MG	JAN 27, 1997 N40236 001
		500MG/15ML:5MG/15ML	N81226 001	<u>AA</u>	панові	Storie, Shi	SEP 25, 1997
			OCT 27, 1992 N89557 001	AA		650MG;7.5MG	N40240 002
		500MG/15ML:5MG/15ML	APR 29, 1992				NOV 26, 1997
	+		N40182 001	AA		650MG; 10MG	N40240 001
AA	PHARM ASSOC	500MG/15ML; 7.5MG/15ML	MAR 13, 1998			750MC.7 EMC	NOV 26, 1997
===				<u>AA</u>		750MG; 7.5MG	N40236 002 SEP 25, 1997
	- 4737			AA	MALLINCKRODT	500MG; 5MG	N40084 002
7	PABLET; ORAL		N89160 001				JUN 01, 1995
**	ANEXSIA MALLINCKRODT	500MG; 5MG	APR 23, 1987	AA		500MG; 7.5MG	N40201 001
AA						E0040 - 1040	FEB 27, 1998
	ANEXSIA 10/660	660MG;10MG	N40084 003	<u>AA</u>		500MG; 10MG	N40201 002 FEB 27, 1998
AA	+ MALLINCKRODT	660mg; Tors	JUL 29, 1996		-	750MG; 7.5MG	N40084 001
	7 5/650		N89725 001	<u>AA</u>			JUN 01, 1995
	ANEXSIA 7.5/650 MALLINCKRODT	650MG; 7.5MG	SEP 30, 1987	AA	+ MIKART	500MG; 2.5MG	N89698 001
<u>AA</u>	MALLINCKKODI		36E 30, 2-0				AUG 25, 1989
	CO-GESIC		N87757 001	<u>AA</u>		500MG; 5MG	N89271 001
AA	SCHWARZ PHARMA	500MG; 5MG	MAY 03, 1982			500MG; 5MG	JUL 16, 1986 N89697 001
				<u> AA</u>		Jourg, Jrig	JAN 28, 1992
	HY-PHEN	500MG; 5MG	N87677 001	AA	+	500MG; 7.5MG	N89699 001
<u>AA</u>	ASCHER		MAY 03, 1982	22	•		AUG 25, 1989
	HYDROCODONE BITARTRATE	AND ACETAMINOPHEN	N40281 001	AA	+	650MG; 7.5MG	N89689 001
3.7	ENDO PHARMS	500MG; 5MG	SEP 30, 1998				JUN 29, 1988
<u>AA</u>	2000	TANKS T EW	N40280 001	AA	n 🛨 mari kata wikimiki Nama kata marikika kata mari	650MG; 10MG	N81223 001 MAY 29, 1992
AA		500MG; 7.5MG	SEP 30, 1998		PEACHTREE	500MG;10MG	N40210 001
		650MG; 7.5MG	N40280 002 SEP 30, 1998	<u>AA</u>	7 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1		AUG 13, 1997
AA		000110,	N40280 003	AA	UCB	650MG; 7.5MG	N40134 001
		650MG; 10MG	SEP 30, 1998				NOV 21, 1996
<u>AA</u>			N40281 002	<u>AA</u>	VINTAGE PHARMS	500MG; 2.5MG	N40144 002
AA		750MG; 7.5MG	SEP 30, 1998			500MG; 5MG	APR 25, 1997 N89831 001
		400MG; 5MG	N40288 001	AA		SOUTH, SER	SEP 07, 1988
		40011070110	NOV 27, 1998 N40288 002	AA	: ************************************	500MG; 5MG	N89971 001
		400MG; 7,5MG	NAU288 002 NOV 27, 1998	***			DEC 02, 1988
			N40288 003	AA		500MG; 7.5MG	N40144 001
		400MG;10MG	NOV 27, 1998			CEONO.7 ENG	FEB 22, 1996
		FOOTO - EMC	N40149 001	<u>AA</u>		650MG; 7.5MG	N40155 001 APR 14, 1997
AA	EON	500MG; 5MG	JAN 27, 1997				MFR 14, 1997

НУ	DROCORTISONE SODIUM SUCC	CINATE		HYDROMORPHONE HYDROCHLORI	<u>DE</u>	
:	INJECTABLE; INJECTION SOLU-CORTEF			INJECTABLE; INJECTION DILAUDID-HP		
AP AP	+ PHARMACIA AND UPJOHN +	EQ 500MG BASE/VIAL EQ 1GM BASE/VIAL	N09866 003 N09866 004	AP + KNOLL PHARM +	10MG/ML 250MG/VIAL	N19034 001 JAN 11, 1984 N19034 002
7732	DDAAADET CAME MAI EDAGE	4		HYDROMORPHONE HCL		AUG 04, 1994
	DROCORTISONE VALERATE CREAM; TOPICAL	•		AP ABBOTT	10MG/ML	N74598 001 JUN 19, 1997
,	HYDROCORTISONE VALERAT			AP STERIS	10MG/ML	N74317 001
AB	COPLEY PHARM	0.2%	N74489 001 AUG 12, 1998			AUG 23, 1995
AB	TARO	0.2%	N75042 001 AUG 25, 1998	SOLUTION; ORAL DILAUDID		
	WESTCORT		·	AA + KNOLL PHARM	5MG/5MIL	N19891 001
<u>AB</u>	+ WESTWOOD SQUIBB	0.2%	N17950 001	HYDROMORPHONE HCL	•	DEC 07, 1992
(OINTMENT; TOPICAL HYDROCORTISONE VALERAT	re		AA ROXANE	5MG/5ML	N74653 001 JUL 29, 1998
<u>AB</u>	TARO	<u>0.2%</u>	N75043 001 AUG 25, 1998	TABLET; ORAL		
	WESTCORT	0.00	•	DILAUDID	0140	
AB	+ WESTWOOD SQUIBB	0.2%	N18726 001 AUG 08, 1983	AB + KNOLL PHARM	8MG	N19892 001 DEC 07, 1992
				AB ROXANE HCL	8MG	N74597 001
HY	DROFLUMETHIAZIDE				pliningsons.	JUL 29, 1998
•	TABLET; ORAL					
AΒ	DIUCARDIN WYETH AYERST	50MG	N83383 001	HYDROXOCOBALAMIN		
AB	HYDROFLUMETHIAZIDE PAR PHARM	50MG	N88850 001	INJECTABLE; INJECTION HYDROXOCOBALAMIN	•	
			MAY 31, 1985	+ STERIS	1MG/ML	N85998 001
AB	+ ROBERTS LABS	50MG	N11949 001	HYDROXYAMPHETAMINE HYDROBI	ROMIDE	
HY	DROFLUMETHIAZIDE; RESERE	PINE		SOLUTION/DROPS; OPHTHALE	MIC	
	TABLET; ORAL			PAREDRINE + PHARMICS	1%	N00004 004
	RESERPINE AND HYDROFLU		200007 001			F00 F0000H
BP	PAR PHARM	50MG; 0.125MG	N88907 001 SEP 20, 1985			
	SALUTENSIN		N12359 003		•	
BP	+ ROBERTS LABS SALUTENSIN-DEMI	50MG; 0.125MG				
	ROBERTS LABS	25MG; 0.125MG	N12359 004			

Exhibit C

We are proposing two formulas for the Hydrocodone Bitartrate and Acetaminophen Elixir 10/325. One will have blue dye and the other will be dye-free.

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR, USP

DESCRIPTION

Hydrocodone Bitartrate And Acetaminophen Elixir, for oral administration, contains hydrocodone bitartrate acetaminophen in the following strengths per 15 mL:

Hydrocodone Bitartrate, USP Acetaminophen, USP

10 mg 325 mg

In addition, the elixir contains the following inactive Ingredients: Alcohol. 7%, Methylparaben, Sodium Saccharin, Sucrose, Propylene Glycol, Glycerin, Sorbitol Solution, and Mixed Fruit Flavor.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5 α -epoxy-3methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, nonsalicylate analgesic and antipyretic. It has the following structural formula:

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating sensors. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

The behavior of the individual Pharmacokinetics: components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak



DESCRIPTION

NORCO* (Hydrocodone bitartrate and acetaminophen) is supplied in tablet form fo

Hydrocodone bitarrate is an opioid analgesic and antitussive and occurs as fine, white or or as a crystalline powder. It is affected by light. The chemical name is 4.5α -epoxy-3-methor methylmorphinan-6-one tarrate (1:1) hydrate (2:5). It has the following structural formula:



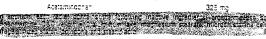
41-mycroxyacatamisde, a slightly bitter, white, odoness, crystalline powde non-opiate, non-salloylate analiges o and antipyretic, it has the following structural formula



Each NORCO ! tablet contains.

Hydrocodona Sitamrate (WARNING, May be habit forming)

10 ma



CLINICAL PHARMACOLOGY

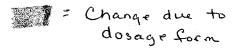
Hydrocodona is a semisymmetro nacquo analgesto and antitussive with multiple at qualitatively similar to mose or occarta. Most of mase involve the central nervous system smooth muscle. The pracisa mechanism of scripn of hydrocodona and other dolates is not kn arthough it is balleyed to relate to the existence of oblate receptors in the central nervous in addition to shalpesia. Percot as may produce drowsiness, changes in mode and

In administration independs of aperaminopher involves peripheral influences, but the so mechanism is as yet undetermined. Antipyretic activity is mediated through hypothelamic regulating centers. Acetaminopher inhibits prostagalating synthetise. Thereforetic dost aperaminopher have regulating participating of the participation of resolutions systems, not toxic doses may cause production failure and hand, shallow breathing.

Pharmacokinetics: The penatror of the individual components is described below

 $\pm .cmcodone$. Following a 10 $\pm .cmc$ oral cose of hydroconone administered to five adult sudjects, the mean deak concentration was 23.6 \pm 5.2 ng/mL. Maximum serum levels

= Brand Name | Generic Nam



concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 \pm 0.3 hours and the half-life was determined to be 3.8 \pm 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α - and 6- β -hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See overdosage for toxicity information.

INDICATIONS AND USAGE

Hydrocodone and acetaminophen elixir is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone, acetaminophen, or any other component of this product.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

Listed Drug

activeed at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydroccol exhibits a complex pattern of metabolism including 3-semethylation. N-demethylation and 3-secont to the apprecedency 6-will an

Acetamingonen: Acetaminoponen is rapidity absorbed from the gastrointestinal tract and distributed throughout most body tesses. The plasma half-life is 1,25 to 3 hours, but may increased by liver damage and following overcosage. Elimination of acetaminophen is orinicial by liver metapolism (consupation) and subsequent renal excretion of metapolities. Approximal 85% of an oral dose appears in the unne within 24 hours of administration, most as gliculronage onlingate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE
NORCO® Tablets are indicated for the relief of moderate to moderately severe pain

CONTRAINDICATIONS

NCRCO F Taclets should not be administered to patients who have previously exhibit hypersansitivity to hydrocadane or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dos related respiratory decression by acting directly on the brain stem respiratory center. Hydrococo also affects the center that controls respiratory rhythm, and may produce irregular and period

Head Injury and Increased Intracranial Pressure; The respiratory depressant effects of narcot and their dapacity to elevate cereorospinal fluid pressure may be markedly exaggerated in the pressure of head injury, other intracranial lesions or a pre-existing increase in intracran pressure. Furthermore, another produce adverse reactions which may obscure the clinical cour of patients with head injuries.

Acute Addominal Candillons: The acministration of narcotics may obscure the diagnosis clinical course of patients with acute accommal conditions.

PRECAUTIONS

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Listed Drug

Special Risk Patients: As with any opioid agent, Hydrocodone Bitartrate anaigesic Acetaminophen Elixir should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all opioids, caution should be exercised when Hydrocodone Bitartrate and Acetaminophen Elixir is used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all opioids, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Patients receiving opioids, Interactions: Drua antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocodone Bitartrate and Acetaminophen Elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

General: <u>Special Risk Patients</u>: As with any narcotic analgesic agent, NORCO® Tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hebatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kect in mind.

<u>Cough reflex:</u> Hydrocodone suppresses the cough reflex: as with all narcotics, caution should be exercised when NORCO[®] Tablets are used postoperatively and in patients with pulmonary disease. Information for Patients: NORCO* Tablets, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, patients should be cautioned accordingly.

Alconol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

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Laboratory Tests: In patients with severe fleoatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Infernations: Patients receiving narrotics, antinistamines, antiosychotics, antianxiety agents or other CNS depressants (including accord) concernitantly with NORCO¹ Tablets may exhibit an additive CNS depression. When combined therapy is contempiated, the dose of one or ooth agents

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Teratogenic Effects: Pregnancy category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone Bitartrate and Acetaminophen Elixir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen elixir may produce constipation.

Teratoganic Effects: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. NORGO: Tacrets should be used buring pregnancy only it the potential benefit justifies the potential risk to the fetus.

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Gastrointestinal System: Protonged administration of NORCO* Tablets may produce constipation.

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Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting on brain stem respiratory centers OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Elixir is classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir is used for a short time = Brand Name (

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued opioid use, although some mild degrees of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by shortened duration of analgesic effect, and subsequently by decreases in the intensity of the analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Serious overdose with hydrocodone is Hydrocodone: characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to

Listed

Genitourinary System: Ureteral spasm, spasm of vesical sphinoters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocogone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE). Dermatological: Skin rasn, pruritus.

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DRUG ABUSE AND DEPENDENCE
Controlled Substance: NORCO® Tablets are classified as a Schedule III controlled substance.

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Physicial dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withcrawal syndrome, assumes clinically significant proportions fonly after several weeks, of continued narcotic use, authough some mid depree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doose are redurted in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE Following an acute overcosage it oxidity may result from hydrocodone or acetaminophen

Signs and Symptoms

Hidrocopone: Serious overcose with hydrocopone is characterized by respiratory decression (a decrease in resolvatory rate and or loal volume. Cheline-Stokes respiration, dyanosis), extreme

Generic Name

stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

In acetaminophen overdosage: dose-Acetaminophen: dependent, potentially fatal hepatic necrosis is the most Renal tubular necrosis, serious adverse effect. hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 - 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdose of less than 10 grams, or fatalities with less than

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended

Immediate treatment includes support of cardio-respiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to Vassopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypo-prothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, an opioid antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A opioid antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Listed Drug

somnoience progressing to studor or doma. Skeletal muscle flacticity, cold and clammy skin, and sometimes, bradycardia, and hypotension. In severe overcosage, aonea, circulatory collabse cardiac arrest and death may occur.

cardiac arrest and death may occur.

Asstaminghen' in acetaminophen overdosage, dose-dependent, potentially fatal hebatic necross is the most serious adverse effect. Renail tubular necrosss, hypogrycemic coma and thrombocytocenia may also occur.

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Treatment: A single or multiple overcose with hydrocodone and acetaminopinen is a potential justical objects, and consultation with a regional poison control center is recommencer. Immediate treatment includes succord of Jactionescriptory function and measures to reduce drug absorption. Vomiting should be included menanically or with syrup of ipector, if the catern is alert (adequate pharyingal and laryingas) retrieves. One accurate chargoal if girkip should foliow gastric emptying. The first does should be accombanied by an accirocrate catination, if recented obes are used, the catination might be included with alternate doses as reduced. Hypotension is usually hypotenemic and should rescond to fluxus. Vasconessors and other succombine measures should be employed as included. A sufficiency activational troe should be incompared and account of the provided assisted recordation. Meticological streams insolud be given to maintaining accessing funding recording the provided assisted recordation. In severe cases of intoxication, personal dialysis, or preferably hemodalysis may be considered, if hypotenemoralized with opening accounts due to accaming one overdose, witamin K should be administered intravendus?

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one out-of- a launce analysis. Can reverse resultancy decreasion and coma associated will opinior overcose. Marokone hyprocondincts of the naisyonal file battert should be keet under of action of hyprocodone may exceed that of the naisyonal file battert should be keet under continuous surreliance and recoated boses of the analysis should be administered as needed to maintain adequate recurrent on A narronno artisponist anould not be administered in the assence of conticony significant respiratory or coroloxascular decreasion.

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If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablespoonful (15 mL) every four to six hours as needed for pain. The total 24-hour dose should not exceed 6 tablespoons.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Elixir is a clear, slightly, fruit flavored liquid containing 10 mg hydrocodone bitartrate, and 325 mg acetaminophen per 15 mL, with 7% alcohol. It is supplied as follows:

10mg/325mg per 15 mL 16 oz. Bottles 4 oz. Bottles 15 mL Unit Dose Cups

NDC 0121-0715-16 NDC 0121-0715-04 NDC 0121-0715-04 NDC 0121-0715-15

Store at controlled room temperature 20 - 25°C (68 - 77°F).

Dispense in a tight, light-resistant container.

R, ONLY

A Schedule III controlled substance

PHARMACEUTICAL ASSOCIATES, INC. Greenville, SC

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Dosage AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

NORCO® is supplied as a yellow, capsule-shaped tablet containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen, bisected on one side and debossed with "NORCO 539" on the other

Bottles of 500 NDC 52544-539-05

Store at controlled room temperature. 15° - 30°C (59° - 86°F). Dispense in a tight, light-resistant container with a child-resistant closure

WATSON PHARMA A Division of Watson Laboratories, Inc. Corona, CA 91720

Revised May 15, 1998

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= change due to dosage form

Controlled Room temperature changed to current usp 24

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HYDROCODONE BITARTRATE ACETAMINOPHEN ELIXIR, USP

DESCRIPTION

Hydrocodone Bitartrate And Acetaminophen Elixir, for oral administration, contains hydrocodone bitartrate acetaminophen in the following strengths per 15 mL:

Hydrocodone Bitartrate, USP Acetaminophen, USP

10 mg 325 mg

in addition, the elixir contains the following inactive aggredients: Alcohol, 7%, Methylparaben, Sodium Saucharin, Sucrosa, Propylene Glycol, Glycerin, Sorbitol Solution, Mixed Fruit Flavor, and FD&C Blue No. 1.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5 α-epoxy-3methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, nonsalicylate analgesic and antipyretic. It has the following structural formula:

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating sensors. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

NORCO® TABLETS

NORCO* (Hydrocodone bitartrate and acetaminopnen) is supplied in tablet form for or

administration.

Hydrocodone bitarirate is an object analgesic and antitussive and occurs as fine, white crysta or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-1 methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:

tetaminophen, 4% proxyeceter line, a slightly bitter, write, oddriess, crystalline downer, s non-opiate, non-salloviate analges cland an cyretic. It has the following structural formula

Each NORCO i tablet contains:

Hydrococche Bitartrate (WARNING, Mai, de nacit forming)

Acetaminophen

325 mg

CLINICAL PHARMACOLOGY

Hypercodding is a semisymmetric motion and gasto and antitussive with multiple action dualitatively similar to mose of opporte. Most of mose involve the central nervous system an smooth muscle. The precise metals and action of hypercoddine and other oblates is not know. A including 1.5 period of reference to the six sterile of coasts redebtors in the central nervous system of addition to analyse 1. Tartition may produce drowsness, changes in mode and men-

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Change due to dosage form

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 5- α- and 6-β-hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by iver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See overdosage for toxicity information.

INDICATIONS AND USAGE

Hydrocodone and acetaminophen elixir is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone, acetaminophen, or any other component of this product.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Listed Drug

Pharmacokinetics: The cenavior of the individual components is described below.

Hydrocogone: Following a 10 mg oral case of thrococodone administered to five adult ma subjects, the mean loeak concentration was 23.5 ± 5.2 ng.m., Maximum serum levels we achieve at 1.3 ± 9.3 hours and the nati-file was determined to be 3.8 ± 9.3 nours. Hydrocodor reduction to the corresponding 6-when including 0-demethylation. N-demethylation and 6-ket See OveRDOSAGE for toward, information.

See OVERDUSAGE for Toxicity information.

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See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

NCRCO® Tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

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WARNINGS
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Listed Drug

Acute abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

Special Risk Patients: As with any opioid General: Hydrocodone Bitartrate analgesic agent, and Acetaminophen Elixir should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all opioids, caution should be exercised when Hydrocodone Bitartrate and Acetaminophen Elixir is used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all opioids, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocodone Bitartrate and Acetaminophen Elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Soecial Risk Patients: As with any narcotic analgesic agent, NORCO® Tablets should be used with caution in elderly or declimated patients, and those with severe impairment of hepatic or renal function, hypothyroidism. Addison's disease, prostatic hypertrophy or urefutal stricture. The usual precautions should be observed and the possibility of respiratory degression should be kept in mind.

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Cardinogenesis, Mutagenesis, Impairment of Fertility, No adequate studies have been conducted in animals to setarmine whether hydrocopone or acetaminognen have a potential for

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Listed Drug

determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

Teratogenic Effects: Pregnancy category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone Bitartrate and Acetaminophen Elixir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. NCRCO: Tablets should be used during pregnancy only it the potential benefit justifies the potential risk to the fetus.

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Labor and Delivery: As with all narcotics, administration of NORCO® Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Adetaminocher is excreted in press milk in small amounts, but the significance of its effects on nursing infatts is not known, it is not known whether hydrocogone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infatts from NGRCO* Tablets, a decision should be made whether to discontinue nursing or to discontinue the arrug, taking into account the importance of the drug to the mother.

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ADVERSE REACTIONS

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> = Brand Name / Generic Name

Product ANDA

Prolonged administration of Gastrointestinal System: hydrocodone bitartrate and acetaminophen elixir may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with

Hydrocodone bitartrate may Respiratory Depression: produce dose-related respiratory depression by acting directly on brain stem respiratory centers OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Hydrocodone Bitartrate and Controlled Substance: Acetaminophen Elixir is classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir is used for a short time for treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued opioid use, although some mild degrees of physical i dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by shortened duration of analgesic effect, and subsequently by decreases in the intensity of the analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Gastrointestinal System: Prolonged administration of NOSCO *Tablets may produce constipation Genitourinary System: Ureteral spasm, spasm of vesicol sphinoters and urinary retention have been reported with objects.

Respiratory Depression: Evolutional bitantrata may produce dose-related respiratory depression by acting directly on orain stem respiratory centers (see OVERDOSAGE). Dermatological: Skin rasn, pruntus.

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Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE
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OVERDOSAGE

Following an acute overcodage, toxicity may result from hydrocodone or acetaminophen Signs and Symptoms

= Brand Name

Generic Name

Product ANDA

Serious overdose with hydrocodone is Hydrocodone: characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

Acetaminophen: In acetaminophen overdosage: dosedependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis. hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 - 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdose of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardio-respiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal Oral activated charcoal (1g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to Vassopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypo-prothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously

Naloxone, an opioid antagonist, can reverse respiratory; depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be

Listed Drug

Hydrocodone: Senous overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or float volume. Cheyne-Stokes respiration, cyanosis), extrema sommolence progressing to stupor or coma, skeletal muscle flacoidity, cold and clammy skin and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collabse, cardiac arrest and death may occur.

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Treatment: A single or multiple overcose with hydrocodone and acetaminoonan is a potentiary tental polygrup overcose, and consultation with a regional coison control center is recommenced. Immediate treatment includes support of radiorespiratory function and measures to reduce drug absorbious Vomiting should be included mechanically, or with syrup of ipecol, if the paramis is aler, lacebase pharyogast and laryogast reflexes). Oral activated charcoal (1) explicit should be accommenced by an abstrootiate charcoal. If recented does should be induced by an abstrootiate charcoal of the processor should be asserted activated by the processor should be accommended by the strootiate of the control of the strootiate of the processor should be inserted abortis grammalia day of the unconscious patient and, when necessary, to provide assisted resolution. Mediculous attention should be given to maintaining adequate pulmonary ventilation in severe cases of intoxication, pertoneal diarysis or preferably hemotrapys may be considered intravenously.

Parageously
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Listed Drug

administered as needed to maintain adequate respiration. A opioid antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablespoonful (15 mL) every four to six hours as needed for pain. The total 24-hour dose should not exceed 6 tablespoons.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Elixir is a bluecolored, fruit flavored liquid containing 10 mg hydrocodone bitartrate, and 325 mg acetaminophen per 15 mL, with 7% alcohol. It is supplied as follows:

10mg/325mg per 15 mL; 16 oz. Bottles 4 oz. Bottles 15 mL Unit Dose Cups

NDC 0121-0716-16 NDC 0121-0716-04 NDC 0121-0716-15

Store at controlled room temperature 20 - 25°C (68 - 77°F).

Dispense in a tight, light-resistant container.

R_x ONLY

A Schedule III controlled substance

PHARMACEUTICAL ASSOCIATES, INC. Greenville, SC

to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

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DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoware effects is dose related.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

HOW SUPPLIED

NORCO so supplied as a yellow, capsule-shapet ablet containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen, bisected on one side and debossed with "NORCO 539" on the other

Bothes of 100 MDC 52544-539-05 Store at controlled room temperature. 15° - 30°C (59° - 86°F). Dispense in a tight, light-resistant container with a child-resistant closure.

WATSON PHARMA A Division of Watson Laboratories, Inc. Corona, CA 91720

Revised May 15, 1998 13095-1

Brand Namel Generic

change due to dosage form

> Controlled Room Temperature changed to current USP 24

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Listed Drug

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR, USP

Hydrocodone Bitartrate (Warning: May be habit forming) and Acetaminophen Tablets, USP

DESCRIPTION

Hydrocodone Bitartrate And Acetaminophen Elixir, for oral administration, contains hydrocodone bitartrate acetaminophen in the following strengths per 15 mL:

Hydrocodone Bitartrate, USP Acetaminophen, USP

10 mg 500 mg

In addition, the elixir contains the following inactive ingredients: Alcohol, 7%, Methylparaben, Sodium Saccharin, Sucrose, Propylene Glycol, Glycerin, Sorbitol, Solution, and Mixed Fruit Flavor, FD&C Yellow No. 10 and FD&C Blue No. 1.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. !t is affected by light. The chemical name is 4,5 α-epoxy-3methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter. white, odorless, crystalline powder, is a non-opiate, nonsalicylate analgesic and antipyretic. It has the following structural formula:

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet Antipyretic activity is mediated through undetermined. hypothalamic heat regulating sensors. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

The behavior of the individual Pharmacokinetics: components is described below.

DESCRIPTION

Hydrocodone bitartrate and acetaminophan is supplied in tablet form for oral administration. Hydrocodone bitartrate is an onloid analysis and antitussive and occurs as fine, white cry or as a crystalline blowder. It is affected by light. The chemical name is 4.5cc-appxy-3-methoxy, methylmorphinan-6-one tartrate (1.1) hydrate (2.5). It has the following structural formula:

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igntly bitter, white, odoriess, drystailine powder layretic, It has the following structural formula: non-porate, non-salicinate analgesic and art

C.H.NO.

MW=151.17

Hydroccoone Sitartrate and Acetaminoptien Tablets, USP for oral apministration are available



CLINICAL PHARMACOLOGY

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Pharmacokinetics: The behavior of the individual components is described below.

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Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 \pm 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α - and 6- β -hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See overdosage for toxicity information.

INDICATIONS AND USAGE

Hydrocodone and acetaminophen elixir is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone, acetaminophen, or any other component of this product.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Listed Drug

Hinrocogos: Following a 10 mg oral dose of hydrocodone administered to five adult in subjects. The mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levets is achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.2 ± 0.3 hours. Hydrocodo exhibits a complex patien of metabolism including 0-demethylation, N-demethylation and 6-seduction to the corresponding 5-4-x and 6-3-hydroxymetabolites.

See OVEROOSAGE for toxicity information

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INDICATIONS AND USAGE

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CONTRAINDICATIONS

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Acute Abcommat Conditions: The acministration of narcotico may obscure the plagnic clinical course of patients with acute accoming conditions.

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PRECAUTIONS

Soecial Risk Patients: As with any opioid agent, Hydrocodone Bitartrate and General: Acetaminophen Elixir should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all opioids, caution should be exercised when Hydrocodone Bitartrate and Acetaminophen Elixir is used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all opioids, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Patients receiving opioids, Drug Interactions: antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocodone Bitartrate and Acetaminophen Elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5hydroxyindoleacetic acid.

Carcinogenésis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

PRECAUTIONS

PRECAUTIONS

General: Sostial Risk Privants 198 in that, in any instruction analyses agent, hydrocodome oitantrate and acetaminophen tapiets should be used with patients agent yor depilitated patients, and those with severe inhorithment of hazar to the security of patients. Addison a disease, prostat hydertrophy or unternat structure. The usual orestances should be observed and the possibility of resonatory decreasion should be resonatory decreasion should be resonated. Addison and the possibility of resonatory decreasion should be resonated with all narrophos, caution should be exercised when hydrocodore outsities and scream nodinant labelets are used postoperatively and in patients with purmonary disease.

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Pregnancy:

Teratogenic Effects: Pregnancy category C: There are no adequate and well-controlled studies in pregnant women. Tydrocodone Bitartrate and Acetaminophen Elixir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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ADVERSE REACTIONS

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Bastrointestinal System: Prolonged administration of sydrocodone bitartrate and acetaminophen elixir may roduce constipation.

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Ргадлалсу:

Teratogenic Effects: Pregnand, Category C. There are no adequate and well-controlled studies pregnant women. Hydrococche cutarnate and academinophen taplets should be used durin pregnand; only it the octential benefit just has the potential risk to the fetue.

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Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting on brain stem respiratory centers OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Elixir is classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir is used for a short time for treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued opioid use, although some mild degrees of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by shortened duration of analgesic effect, and subsequently by decreases in the intensity of the analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to

Genitourlinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respirat decression by acting directly on brain stem respiratory centers (see OVERDOSAGE). Dermatological: Skin rash, pruntus,

The following adverse drug events may be come in mind as potential effects of adetaminocial argumentations, rash, thrombooytopenia, agranulocytosis.

Forential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocoone Bitarriate and Acetaminophen Tablets are classified a Schedule III controlled substance.

Schedule II controlled substance.

Abuse and Dependence: Psychic decendence, physical decendence, and tolerance may devict research administration of narcotics, therefore, this product should be prescribed administration. However, psychic decendence is unifixely to develop when hydrocop bisanciate and acetaminophen tablets are used for a short time for the treatment of zon. Psystal decendence, the condition in which continued administration of the drug is recit to revent the accessors. Of continued narrotic use, altituding some mitid degree of enjoy ceancerise may develop after a few days of narcotic these above the drug is manifested in the first accessors are recurred in order to produce the same degree of analysis as a recurred in order to produce the same degree of analysis as manifested in by a sometime duration of analysis defect, and subsequently by decreases in the intensit analysis. The rate of dereciment of forerance varies among observing

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminochen

= Brand Name 1 Generic Name

Product ANDA

stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

Acetaminophen: In acetaminophen overdosage: dosedependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis. hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 - 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdose of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose. and consultation with a regional poison control center is

immediate treatment includes support of cardio-respiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to Vassopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. in severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypo-prothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, an opioid antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A opioid antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Listed Drug

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Anesthingchem: In acetaminochem overcosage: dose-decendant, octantially fatal medius necro
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Listea Drug

f the dose of acetaminophen may have exceeded 140 ng/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour ntervals

Methemoglobinemia over 30% should be treated with nethylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and esponse of the patient. However, it should be kept in mind hat tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose elated.

The usual adult dosage is one tablespoonful (15 mL) every our to six hours as needed for pain. The total 24-hour dose should not exceed 6 tablespoons.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Elixir is a greencolored, fruit flavored liquid containing 10 mg hydrocodone pitartrate, and 500 mg acetaminophen per 15 mL, with 7% alcohol. It is supplied as follows:

10mg/500 mg per 15 mLt. 16 oz Bottles NDC 0121-0717-16 NDC 0121-0717-04 15 mL Unit Dose Cups NDC 0121-0717-15

Store at controlled room temperature 20 - 25°C (68 - 77°F).

Dispense in a tight, light-resistant container.

R, ONLY

A Schedule III controlled substance

PHARMACEUTICAL ASSOCIATES, INC. Greenville, SC

02/00

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2.5 mg/500 mg 5 mg/500 ma

the usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets. The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets. The usual adult dosage is one of two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets. 7.5 mg/500 mg 7.5 ma/750 ma

7.5 mg/650 mg

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HOW SUPPLIED

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Serias vi 300 MCC 52544-387-06 Borras vi 1000 NCC 52544-387-10 7,5 mg meropodene biturrate and 650 mg acetaminophen coostie shaped mink society tradition on what side and 3600sed with Walson

10 mg hydrocodone bitactate and 650 mg dceraminophen, capsule-straced light green bitacts bisected on one side and debossed with Watson 503 on the other side. Bortles of 100 NDC 52544-503-01 Bortles of 100 NDC 5254-503-05

Store at controlled room temperature: 1512 30 0 (153 38 0). Dispense in a tight, light-resistant container with a child-resistant closure.

Watson Laboratories Corona, CA 91720

C mg/500 mg

Revised December 15, 1997 13100-1

Brand Name/Generic Name

change due to dosage form

Controlled Room Temperature changed to current USP 24

HYDROCODONE **BITARTRATE** AND ACETAMINOPHEN ELIXIR, USP

DESCRIPTION

Hydrocodone Bitartrate And Acetaminophen Elixir, for oral administration, contains hydrocodone bitartrate acetaminophen in the following strengths per 30 mL:

Hydrocodone Bitartrate, USP Acetaminophen, USP

10 mg 650 mg

in addition, the elixir contains the following macing ingredients: Alcohol, 7%, Methylparaben, Sodiain Saccharin, Sucrosa, Propylene Glycol, Glycerin, Solibitol Solution, and Mixed Fruit Flavor.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4.5α -epoxy-3methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, nonsalicylate analgesic and antipyretic. It has the following structural formula:

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating sensors. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

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Listed Drug

Hydrocodone Bitartrate (Warning: May be habit forming) and Acetaminophen Tablets, USP



Hydrocodone bitanrate and acetaminophan is supplied in tablet form for oral administration.
Hydrocodone bitanrate is an occition analysis and antitussive and occurs as fine, white cryst,
or as a crystalline powder. It is affected by fight. The chemical name is 4,54-eepoxy-4,64-enoxy-1,
methylmoropinan-6-one tarrate (1,1) nydrate (2,5). It has the following structural formula:

MW=494 50

Acetaminophen 4 ingromysceramilde, a slightly bitter, white, oddriess, crystalline powder is non-sairbjars analgesic and antiogresic. It has the following structural formula:

MW=151.17

Nydroccoone Sitamate and Acetaminophen Tablets, USP for oral administration are available in variety of strengths as described below: Hydroccoone Sitamate

CLINICAL PHARMACOLOGY

Hydrococone is a semisynthetic narrotto enalged and antitussive with multiple action quantitiative similar to those of receive. Most of these involve the central nervous system as smooth muscle. The precise mechanism of action of hydrococone and other opitates is not know although its place-before relate to the existence of opitate receiptors in the central nervous system in addition to analgesia, narrottos that, propose drowstness, changes in mood and metri-

In action to analysis, machine may missively perpensis influences, but the specificating. The analysis action of acetaminopnes involves perpensis influences, but the specificacination is as yet uncertamined. Antiopratio activity is mediated through hypothalamic her requiating centers. Acetaminopnes inhibits prostaglandin synthetiae. Therapeatic doses of acatimicones have negligible effects on the cardiovascular or resolvatory systems; however taxed observances any causes provided the analysis of the individual components is described below.

= Brand Name 1 Generic Name

change due to dosage form

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α - and 6-β-hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See overdosage for toxicity information.

INDICATIONS AND USAGE

Hydrocodone and acetaminophen elixir is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone, acetaminophen, or any other component of this product.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Listed Drug

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Listed Drug

PRECAUTIONS

Special Risk Patients: As with any opioid agent, Hydrocodone Bitartrate and General: analgesic Acetaminophen Elixir should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all opioids, caution should be exercised when Hydrocodone Bitartrate and Acetaminophen Elixir is used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all opioids, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocodone Bitartrate and Acetaminophen Elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-1 hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: (No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

PRECAUTIONS

PREJUITION

General: <u>Scarta: Risk Patients</u> is not any, natroit analysis agent, hydrocodone bitartrara and acetaminophen tablets should be used with sound in elderly or debilitated patients, and those with severe imperment of health or rene function injustic, routism. Addison's disease, prostatility performing or retiral structure. The use or resultance should be observed and the possibility or resouratory decreasion should be rest in 70.00.

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Pregnancy:

Teratogenic Effects: Pregnancy category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone Bitartrate and Acetaminophen Elixir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on jursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many trugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants rom hydrocodone and acetaminophen, a decision should be hade whether to discontinue nursing or to discontinue the arug, taking into account the importance of the drug to the nother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, ethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of nydrocodone bitartrate and acetaminophen elixir may produce constipation.

Listed Drug

Pregnancy: Treatogenic Effects: Pregnancy, Caragon, C. There are no adequate and well-controlled studies - pregnant women. Hydrococons obtained and acetaminophan tablets should be used during pregnancy any a the octential basis has been acetaminophan tablets should be used during Pregnancy any a the octential basis has been acetaminophan tablets should be used during Pregnancy any at the octential basis been to more switch have been tabling denoids requiring transfers mit be physically dependent. The withortawal signs include irritability and excessive crying transfers, hyperactive reflexes, increased restricting rate, increased stoods, sneezing, yawhing womiting and lever. The intensity of first performed does not always correlate with the duration of material ording of this product to the outputs of the product to the product of the

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Gastrointestinal System: Prolonged acrumistration of hydrocodone bilartrate and acetaminocner taciets may produce constitution.

= Brand Name / Generic Name

ANDA Product

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Hydrocodone , Bitartrate and Controlled Substance: Acetaminophen Elixir is classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir is used for a short time for treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued opioid use, although some mild degrees of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by shortened duration of analgesic effect, and subsequently by decreases in the intensity of the analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Serious overdose with hydrocodone is Hydrocodone: characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to

Listed Drug

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Signs and Symptoms

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Product ANDA

stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

Acetaminophen: In acetaminophen overdosage: dosedependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 - 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdose of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardio-respiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to Vassopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypo-prothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, an opioid antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A opioid antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Maria and M

Listed Drug

sommolence progressing to studor or comal skeletal muscle flacdicity cold and claimity skip, an sometimes bradycardia and hypotension. In severe overdosage, apneal circulatory collaboractics arrest and death maj occur.

carding arrest and death may occur.

Anstamingthem in agetamingthem overcosage; dose-dependent, obtainably tatal hebatic necros is the most serious adverse effect. Rehall tubular necrosis, hypoglycemic coma an thromodytopenia may also occur.

Early symptoms following a potentia, y necutotoxic overcose may include, nauses, womicing diaphoresis and general malase. Clinical and laboratory evidence of hebatic toworty may not clacosard until 45 to 72 hours obstraigestion.

In pollis, hebatic following may rare gray, deen reported with abute overcoses of less than 10 gram or fatalities with less than 15 grams.

or latalities with less than 15 grams.

Treatment A single or militude overcose with hydrocodone and acetaminophen is a potential lethal polydrug overcose. End consultation with a regional poison control center is recommended immediate treatment includes support of cardiorestiratory function and measures to reduce displaying the proposed of the center is elemantation. Or with syrup of libecologistic fifthe parties silen ladequate ponaryinges and languages reflexes. Oral activated charcoat (1 grkg should folio gastrio emptying. Tha first loss should be accompanied by an appropriate cathartic. If repair doses are used, the cathartic might be nacioned with alternate doses as required, Hypotension usually hypovolemic and should respons to fluids, Vasopressors and other supportive measure should be emotoyed as indicated. A collection and the should be inserted before gestillating of the unconscious datent and, when necessary, to provide assisted respiration. Meticologis attention should be demonstrated in the should be inserted before gestillating of the unconscious datentiand, when necessary, to provide assisted respiration. Meticologis attention should be demonstrated intoxication, personal disaysis, or preferably hemocratysis may be considered hypoporothromothiomenial occurs due to acetaminophen overgose, vitamin K should be administers introverboosty.

Narozone, a narcotic antagonist, can reverse respiratory decression and coma associated will occid overdose. Naroxone hyprochloride 0.4 mg to 2 mg is given parenterally. Since the duratic or action of hydrococone may exceed that of the natoxone, the patient should be kept uncl. continuous surveillance and received doses of the antagonist should be administered as needs to maintain adequate resolutation. A narcotic antagonist should not be administered in the abser of clinically significant resolutatory or cardiovascular decression.

ANDA Product

Listed Drug

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is two tablespoonfuls (30 mL) every four to six hours as needed for pain. The total 24-hour dose should not exceed 6 tablespoons.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Elixir is a clear, fruit flavored liquid containing 10 mg hydrocodone bitartrate, and 650 mg acetaminophen per 30 mL, with 7% alcohol. It is supplied as follows:

10mg/650 g	na per 30 ml				
16 by Bottl	ng per 30 mL es		NDC	0121-07	18-16
4 oz Bottle	Strawn and resident	e de graja de cias, pa	NOC	0121-07	18-04
30 mL Unit	Dose Cups	778	NDC	0121-07	18-30
THE PERSON NAMED IN COLUMN	was bridge and the control	A STATE OF THE PARTY OF THE PARTY OF THE	P. C.		The statement in

Store at controlled room temperature 20 - 25°C (68 - 77°F).

Dispense in a tight, light-resistant container.

R_x ONLY

KARANTAN MARKATAN

A Schedule III controlled substance

PHARMACEUTICAL ASSOCIATES, INC. Greenville, SC

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially and repeated at 24-hours intansie. initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets. The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets. 2.5 mg/500 mg 5 mg/500 mg

7.5 ma/500 ma

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets. The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 5 tablets. 7.5 mg/750 mg 7.5 mg/650 mg

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets. 10 mg/500 mg The usual adult dosage is one tablet every four to six hours as needed for

pain. The total daily dosage should not exceed 6 tablets.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets. 10 mg:650 mg

HOW SUPPLIED

Hydrocodone Bitartrate (WARNING: May be habit forming) and Adetaminophen Tablets are

rties of 500 / CC 52511-388-05 Ties of 7000 / CC 52544-388-10

Sign 100 S2531-360-10 mg acetamnophen hydrocodone brattate and 500 mg acetamnophen his 2 sign 5 schol on one class and debosee un other one side \$17.00 S2531-340-36 5 mg 500 mg

TOO NDC 5254-346-36
SEC NDC 5254-366-366
SEC NDC 5254-366
SEC NDC 5254-

7.5 mg nythrodoone bisinfate and 650 mg acataminophen, capsule-shaped prink tablers bisected on one side and debossed with Watson 502 on the other side. 7.5 mg 550 mg

10 mg/500 mg

NDC 52544-540-85

10 mg hydrocodone bitarrate and 650 mg acetaminophen, capsule-shaced light green bblists biselted oncore side and debossed with Watson 503 on the other side.

80thes of 100 NDC 52544-501-01 10 mg/650 mg NDC 52544-503-01 NDC 52544-503-05 NDC 52544-503-05

Stories of 500 NDC 52544-503-07 Store at controlled room temperature, 15 * 30°C (55° 86°F).
Dispense in a tight, light-resistant container with a child-resistant closure

Watson Laboratories Revised December 15, 1997 13100-1

Corona, CA 91720

7.5 mg:500 mg

7.5 ma 750 ma

Brand Name | Generic Name

02/00

hanged due to dosage form

Controlled Room Temperature changed to current USP 24

Exhibit D

ANDA Product

Listed Drug

FRONT OF LABEL:

NDC 0121-0716-16

. HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg/325 mg per 15 mL

Hydrocodone bitartrate, USP (Warning: May be habit forming) Acetaminophen, USP Alcohol 7%

10 mg 325 mg

Alcono. R, ONLY Ho fl oz (473 mE)

PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information. Lot No. Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required). Store at controlled room temperature 20° - 25° C (68° - 77° F)

NOC 52544-539-01 NORCO™ hydrocodone bicartrate and acetaminophen tablets, USP

10 mg/325 mg ACHTABLET CONTAINE

Bitarrile USP....10 mg

CAUTION: Federal law prohibits dipensing without prescription.

(WATSON

Dispense in a tight, light-resistant container with a child-resistant closure.

USUAL ADULT DOSAGE: One tablet every four to six lours, as needed for pain. Total daily do:age should not

See insert for full prescribing information.

Keep this and all medication out of the reach of children. Store at controlled room temperatur: 15°-30°C (59°-86°?).

EXP.:

Brand Name | Generic Name

= change due to dosage form

Controlled Room Temperature changed to Current use 24

ANDA Product

Listed Drug

FRONT OF LABEL:

NDC 0121-0718-16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg/650 mg per 30 mL

Hydrocodone bitartrate, USP (Warning: May be habit forming) Acetaminophen, USP Alcohol 7 % R, ONLY 10 mg

650 mg

16 fl oz (473 mL)»

PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information. Lot No. Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Store at controlled room temperature

20° - 25° C (68° - 77° F)



= Brand Name | Generic Name

= change due to dosage form

= Controlled Room Temperature Changed to current USP 24 Delivers 15 mL NDC 0121-0717-15

Hydrocodone Bitartrate and CIII
Acetaminophen Elixir

10 mg/500 mg per 15 mL

Alcohol 7%

Usual Dosage: See Package Insert for Complete Dosage Recommendations.

(Lot No. and Exp. Date)

R, ONLY
FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

Delivers 30 mL NDC 0121-0718-30

Hydrocodone Bitartrate and Acetaminophen Elixir

CIII

10 mg/650 mg per 30 mL

Alcohol 7%

Usual Dosage: See Package Insert for Complete Dosage Recommendations.

(Lot No. and Exp. Date)

R, ONLY FOR INSTITUTIONAL USE ONLY PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605 Delivers 15 mL NDC 0121-0716-15

Hydrocodone Bitartrate and Acetaminophen Elixir

CIII

10 mg/325 mg per 15 mL

Alcohol 7%

Usual Dosage: See Package Insert for Complete Dosage Recommendations.

(Lot No. and Exp. Date)

R, ONLY
FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

Delivers **15 mL** NDC 0121-0715-15

Hydrocodone Bitartrate and Acetaminophen Elixir

CIII

10 mg/325 mg per 15 mL

Alcohol 7%

Usual Dosage: See Package Insert for Complete Dosage Recommendations.

(Lot No. and Exp. Date)

R, ONLY
FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

NDC 0121-0717-15

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

10 mg/500 mg per 15 mL

Alcohol 7%

Preservative: Methylparaben 0.15%

pH Range: 4.0 - 5.0

Usual Dosage: See Package Insert for Complete Dosage Recommendations.

 $10 \times 15 \text{ mL}$

This unit-dose package is not child-resistant. Store at controlled room temperature,

20° - 25° C (68° - 77° F)

R. ONLY

FOR INSTITUTIONAL USE ONLY PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

NDC 0121-0718-30

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

10 mg/ 650 mg per 30 mL

Alcohol 7%

Preservative: Methylparaben 0.15%

pH Range: 4.0 - 5.0

Usual Dosage: See Package Insert for Complete Dosage Recommendations.

 $10 \times 30 \text{ mL}$

This unit-dose package is not child-resistant. Store at controlled room temperature,

20° - 25° C (68° - 77° F)

R, ONLY

FOR INSTITUTIONAL USE ONLY PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605 NDC 0121-0716-15

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

10 mg/325 mg per 15 mL

Alcohol 7%

Preservative: Methylparaben 0.15%

pH Range: 4.0 - 5.0

Usual Dosage: See Package Insert for Complete Dosage Recommendations.

 $10 \times 15 \text{ mL}$

This unit-dose package is not child-resistant. Store at controlled room temperature,

20° - 25° C (68° - 77° F)

R. ONLY

FOR INSTITUTIONAL USE ONLY

PHARMACEUTICAL ASSOCIATES, INC.

GREENVILLE, SC 29605

NDC 0121-0715-15

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

10 mg /325mg per 15 mL

Alcohol 7%

Preservative: Methylparaben 0.15%.

pH Range: 4.0 - 5.0

Usual Dosage: See Package Insert for Complete Dosage Recommendations.

 $10 \times 15 \text{ mL}$

This unit-dose package is not child-resistant. Store at controlled room temperature,

re at controlled room temperat

20° - 25° C (68° - 77° F)

R, ONLY

FOR INSTITUTIONAL USE ONLY

PHARMACEUTICAL ASSOCIATES, INC.

GREENVILLE, SC 29605 NDC 0121-0715-15

NDC 0121-0717-16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg/500 mg per 15 mL

Hydrocodone bitartrate, USP (Warning: May be habit forming)

10 mg

Acetaminophen, USP

500 mg

Alcohol 7%

R, ONLY

16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information. Lot No. Exp. Date

LEFT SIDE OF LABEL:

NDC 0121-0716-16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg/325 mg per 15 mL

Hydrocodone bitartrate, USP (Warning: May be habit forming)
Acetaminophen, USP
Alcohol 7 %
R, ONLY

10 mg

325 mg

16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information. Lot No. Exp. Date

LEFT SIDE OF LABEL:

NDC 0121-0715-16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg/325 mg per 15 mL

Hydrocodone bitartrate, USP

10 mg

(Warning: May be habit forming)

Acetaminophen, USP

325 mg

Alcohol 7% R, ONLY

16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information. Lot No. Exp. Date

LEFT SIDE OF LABEL:

NDC 0121-0718-16

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg/650 mg per 30 mL

Hydrocodone bitartrate, USP
(Warning: May be habit forming)
Acetaminophen, USP
Alcohol 7 %
R, ONLY

10 mg

650 mg

16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information. Lot No. Exp. Date

LEFT SIDE OF LABEL:

NDC 0121-0717-04

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg/500 mg per 15 mL

Hydrocodone bitartrate, USP (Warning: May be habit forming)
Acetaminophen, USP

500 mg

10 mg

Alcohol 7% R. ONLY

4 fl oz (118 mL)

PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information. Lot No. Exp. Date

LEFT SIDE OF LABEL:

NDC 0121-0716-04

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg/325 mg per 15 mL

Hydrocodone bitartrate, USP

10 mg

(Warning: May be habit forming)

Acetaminophen, USP

325 mg

Alcohol 7% R, ONLY

4 fl oz (118 mL)

PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information. Lot No. Exp. Date

LEFT SIDE OF LABEL:

NDC 0121-0715-04

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg/325 mg per 15 mL

Hydrocodone bitartrate, USP 10 mg (Warning: May be habit forming)
Acetaminophen, USP 325 mg
Alcohol 7 %

R_x ONLY

PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

4 fl oz (118 mL)

USUAL DOSAGE: See package insert for complete prescribing information. Lot No. Exp. Date

LEFT SIDE OF LABEL:

NDC 0121-0718-04

HYDROCODONE BITARTRATE AND ACETAMINOPHEN ELIXIR

CIII

10 mg /650 mg per 30 mL

Hydrocodone bitartrate, USP (Warning: May be habit forming)
Acetaminophen, USP
Alcohol 7 %
R, ONLY

10 mg

650 mg

4 fl oz (118 mL)

PHARMACEUTICAL ASSOCIATES, INC. GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert for complete prescribing information. Lot No. Exp. Date

LEFT SIDE OF LABEL:

Exhibit E

Hydrocodone bitartrate and Acetaminophen Elixir (NDC 0121-0715-) has been packaged in the following container/closure systems:

- Bottle: 16 oz. Amber PET 28-400 container
 Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
- 2. Bottle: 16 oz. Amber PET 28-400 container
 Cap: 28-400 White Fine Ribbed Closure with SG-90 Liner
- 3. Bottle: 16 oz. Brown HDPE BL-16 container
 Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
- 6. Bottle: 4 oz. Amber PET 24-400 container
 Cap: 24-400 White Clic-Loc with P/RVTLF Liner
- 7. Unit Dose Cup: BP 15 HDPE Unit Dose Container made of Alathon resin. Lidding: Paper/Polyethylene/Aluminum Foil/Heat Seal by Tekni-Plex

Hydrocodone bitartrate and Acetaminophen Elixir (NDC 0121-0716-) has been packaged in the following container/closure systems:

- Bottle: 16 oz. Amber PET 28-400 container
 Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
- Bottle: 16 oz. Amber PET 28-400 container
 Cap: 28-400 White Fine Ribbed Closure with SG-90 Liner
- 3. Bottle: 16 oz. Brown HDPE BL-16 container
 Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
- 6. Bottle: 4 oz. Amber PET 24-400 container
 Cap: 24-400 White Clic-Loc with P/RVTLF Liner
- 7. Unit Dose Cup: BP 15 HDPE Unit Dose Container made of Alathon resin. Lidding: Paper/Polyethylene/Aluminum Foil/Heat Seal by Tekni-Plex

Hydrocodone bitartrate and Acetaminophen Elixir (NDC 0121-0717-) has been packaged in the following container/closure systems:

- Bottle: 16 oz. Amber PET 28-400 container
 Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
- 2. Bottle: 16 oz. Amber PET 28-400 container
 Cap: 28-400 White Fine Ribbed Closure with SG-90 Liner
- 3. Bottle: 16 oz. Brown HDPE BL-16 container
 Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
- 6. Bottle: 4 oz. Amber PET 24-400 container Cap: 24-400 White Clic-Loc with P/RVTLF Liner
- 7. Unit Dose Cup: BP 15 HDPE Unit Dose Container made of Alathon resin. Lidding: Paper/Polyethylene/Aluminum Foil/Heat Seal by Tekni-Plex

Hydrocodone bitartrate and Acetaminophen Elixir (NDC 0121-0718-) has been packaged in the following container/closure systems:

- Bottle: 16 oz. Amber PET 28-400 container
 Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
- Bottle: 16 oz. Amber PET 28-400 container
 Cap: 28-400 White Fine Ribbed Closure with SG-90 Liner
- Bottle: 16 oz. Brown HDPE BL-16 container
 Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
- 6. Bottle: 4 oz. Amber PET 24-400 container Cap: 24-400 White Clic-Loc with P/RVTLF Liner
- 7. Unit Dose Cup: BP 15 HDPE Unit Dose Container made of Alathon resin. Lidding: Paper/Polyethylene/Aluminum Foil/Heat Seal by Tekni-Plex

201 DELAWARE STREET GREENVILLE SC 29605

1 OF 1

SHIP TO: DOCKETS MANAGEMENT
HFA-305
FOOD & DRUG ADMINIS
5600 FISHER LANE, RI
ROCKVILLE, MD



(420) SHIP TO POS



UPS NEXT DAY AIR

TRACKING *: 1Z 221 911 01 0000 5810



PO# 4495